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COMMISSION ON EPIDEMIOLOGICAL SURVEY

ARMED FORCES EPIDEMIOLOGICAL BOARD

SUMMARY OF THE ANNUAL REPORT

OF THE COMMISSION

FISCAL YEAR 1967

AD828660

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ARMED FORCES EPIDEMIOLOGICAL BOARD

SUMMARY OF THE ANNUAL REPORT

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FISCAL YEAR 1967

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12. ABSTRACT Summaries of presentations made at the Symposium on Infection and Metabolism sponsored by the Commission in September 1967 are presented. Presenters are listed above as authors. The Symposium was held at the time of the annual meeting. The entire Symposium is published as a Special Report.		
13. KEYWORDS: Amino acids Metabolism Infections Circadian periodicity Newcastle disease virus Tularemia Salmonellosis Enzymes <u>Diplococcus pneumoniae</u> Sandfly fever RNA DNA Tissue culture Protein synthesis Nucleic acids Antibody		

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THE DIRECTOR'S SUMMARY REPORT

The Annual Meeting of the Commission on Epidemiological Survey was held at the Walter Reed Army Institute of Research on 7 and 8 September 1967. The two day meeting was devoted to a Symposium on Infection and Metabolism which was attended by Commission members, representatives of the Military Services, distinguished scientific contributors to the program and guests:

U. S. Army Medical Unit

Colonel William R. Beisel, MC
Captain Martha K. Ward, USPHS
Lt Colonel Peter J. Bartelloni, MC
Lt Colonel Stewart McConnell, VC
Major George E. Shambaugh, III, MC
Captain John M. Kehoe, VC
Captain Albert S. Klainer, MC
Captain Robert E. Krisch, MC
Captain Sigurd J. Normann, MC
Captain Robert S. Pekarek, MSC
Captain David G. Van Ormer, MSC
Captain Earl J. Wright, MC
Dr. Virginia G. McGann

U. S. Army

Colonel Donald L. Howie, MC, Medical Research & Development Command
Colonel Stefano Vivona, MC, Walter Reed Army Institute of Research
Lt Colonel Robert Cutting, MC, Medical Research & Development Command
Lt Colonel John Kinarson, Office of the Surgeon General
Lt Colonel Robert L. Krivulka, Medical Research & Development Command
Captain O. T. Danhaus, Jr., Walter Reed Army Institute of Research
Captain Edward F. Moroney, MC, Medical Research & Development Command

U. S. Navy

Commander Charles N. Miller, MC, Bureau Medicine and Surgery
Ensign Robert P. Nalewaik, MSC, Fort Detrick

U. S. Air Force

Captain Amos R. Townsend, Office of The Surgeon General

Guests

Dr. Hilton B. Levy, National Institutes of Health
Dr. Elisha Atkins, Yale University
Dr. Paul M. Newberne, Massachusetts Institute of Technology
Dr. Robert L. Squibb, Rutgers University
Dr. Vernon R. Young, Massachusetts Institute of Technology
Dr. Elliot M. Levine, Albert Einstein College
Dr. John M. Woodward, University of Tennessee
Dr. Paul C. Zamecnik, Harvard University
Dr. Peter F. Bonventure, University of Cincinnati
Dr. Morton I. Rapoport, University of Maryland
Dr. Irving Gray, Georgetown University
Dr. Adam J. Rapalski, National Research Council
Dr. Hamish N. Munro, Massachusetts Institute of Technology
Dr. Sidney H. Ingbar, Thorndike Memorial Laboratory
Dr. Herbert L. DuPont, University of Maryland
Dr. Harold N. Glassman, Fort Detrick
Dr. Joseph E. Johnson, University of Florida
Dr. Bernard du Buy, University of Maryland
Dr. N. V. Barzauskos, University of Maryland
Dr. Frank A. Carozza, Jr., University of Maryland
Dr. Walter W. Kemmener, National Air Space Administration
Dr. Samuel Bessman, University of Maryland

Unavoidable conflicts prevented Dr. Gustave J. Dammin, President of the Armed Forces Epidemiological Board, from attending; he was ably represented by Dr. John E. Craighead. Captain Sidney A. Britten, USN, Executive Secretary of the Board, and Administrative Assistant, Miss Betty Gilbert, were cited for their unstinting assistance which makes it possible to conduct the Commission's affairs.

After introductory remarks by Colonel William R. Beisel and the Director, the two days were devoted to the scientific agenda and discussions. Colonel Dan Crozier was particularly cited for his foresight and attention to administrative details which made the Symposium possible. Because of illness he was unable to attend the meeting.

The U. S. Army Medical Unit, working in collaboration with scientists at Fort Detrick during the year, made significant contributions pertinent to better understanding of the pathogenesis of certain specific infectious diseases and provided leads to earlier etiologic detection.

AMINO ACID AND ENZYME ALTERATIONS

Among these studies is the demonstration that whole blood amino acids show circadian periodicity with values lowest at 0400 hours and highest between 1200 and 2000 hours. In controlled human infections, such as typhoid fever, blood amino acid values are lower during the incubation

period of those persons who subsequently become clinically ill; concentrations increase during the active disease. Although there are no distinctive diagnostic patterns, there are valuable leads involving single and total amino acid changes in typhoid fever, Venezuelan equine encephalitis and after vaccination with 17-D yellow fever vaccine. Related biochemical studies showed that induced pneumococcal infection in mice produced alterations in liver protein anabolism, specifically, tryptophan pyrrolase, a specific liver enzyme. Changes in enzyme synthesis and total hepatic protein anabolism occur very early in infection and such biochemical reactions presumably precede the onset of illness. Urinary diazo formation is related to tryptophan metabolism through niacin pathways. Urinary diazo reactants were demonstrated early in the course of human sandfly fever. Interpretation of enzymatic abnormalities are fraught with difficulties since techniques require standardization; valuable leads are being developed.

CELLULAR NUCLEIC ACID CHANGES

During Diplococcus pneumoniae infection of mice, increased synthesis of RNA occurred 24 hr postinoculation with values below control levels in the agonal stages. In virulent arbovirus infections of mice depression of RNA synthesis occurs. The relationship of these findings to pathogenesis is unknown. Interpretation of studies of increase or decrease in RNA synthesis requires evaluation of whether cells are in a resting or growing phase. Double stranded RNA has the capacity to increase the rate of interferon in cells which increases host resistance to virus infections.

DETECTION OF EARLY ANTIBODY, ANTIGEN AND GAMMA GLOBULINS

Using the Jerne antibody plaque technique and identification of RNA in cells with acridine orange and other stains, it has been shown that cells begin to form antibody about 5 hr after the antigenic stimulus. Studies directed to early identification of circulatory antigen show promise. Latex particles sensitized with pneumococcus antisera show good specificity particularly when particles are incubated at 4 C. This reaction antedates the demonstration of bacteremia.

Studies have been initiated to determine the patterns of immune globulin response in volunteers given $10^{7.5}$ mouse IC_{LD50} doses of 17-D yellow fever virus as the primary exposure. Titers of IgM, IgG, IgA are being evaluated.

HORMONAL RESPONSES IN INFECTIONS

Metabolic responses are altered in specific infections. Unbound thyroxine increases with infection before onset of fever in tularemia and returns to normal before defervescence. Thyroxine disposal begins several days after onset of clinical illness and PBI rises in the early recovery period. These and other results suggest that thyroxine exerts an anabolic effect during infection. In mice infected with pneumococci, plasma corticosteroid levels increase about 4 hr before those of plasma thyroxine.

A rather stereotyped pattern of adrenal response occurs in certain acute infectious illnesses. Glucocorticoid hormone output increases before or simultaneously with onset of symptoms; plasma 17-OHCS concentrations lose their afternoon diurnal fall and remain slightly above early morning levels. Mild infections fail to alter adrenal response; severe and protracted infections are associated with depressed adrenocortical output. Studies of protein synthesis and enzyme induction in animal infections suggest that endogenous glucocorticoids benefit the host by stimulating increased protein anabolism within the liver.

TRACE METALS AND SERUM PROTEIN CHANGES

Evaluation of trace metal changes have shown depression of urinary Zn output at the onset of human tularemia and Q fever and subsequent excess excretion in the postfebrile period. Other clues of early change are that serum glycoglobulins appear earlier in infection and are more specific than routine serum proteins. Alpha glycoglobulins are decreased in mice and rats within 12-16 hr after pneumococcal infection. Contrariwise, they are increased in humans prior to and simultaneous with the onset of tularemia. Conceivably, patterns may be identified as specific indicators of etiology in the early stages of infection.

LOCALIZATION OF STAPHYLOCOCCAL ENTEROTOXIN

Staphylococcal enterotoxin B (SEB) injected intravenously in rats and monkeys is rapidly removed by renal clearance. Fluorescent labeled and unlabeled toxin localizes in proximal renal convoluted tubules; smaller amounts appear in the liver and gastrointestinal tract. Toxin may gain access to the tubules via glomerular filtration and tubular reabsorption.

The Commission, through the University of Maryland Contract, has extended the studies of vaccines and pathogenesis, including physiologic effects, of toxins.

Q FEVER VACCINE EVALUATION

The influence of phase variation in Q fever vaccines has continued. Thirty-five hundred GPIPJD₅₀ of Coxiella burnetii aerosolized as a "static cloud" will cause disease in volunteers with an incubation period of about 10-12 days. Phase I vaccine gave more protection to exposed volunteers than did Phase II. Of 19 volunteers challenged 5-8 months after Phase I vaccination, 2 developed disease. Two of 5 volunteers who had received Phase II vaccine became ill. One Phase I vaccinee was challenged 36 months after receiving a single 30 mg dose of the vaccine. He developed a low grade persistent fever requiring tetracycline therapy.

Three Rocky Mountain spotted fever convalescents developed unmodified Q fever after exposure to C. burnetii.

There have been 4 separate trials with viable Q fever. Illness was produced in 11 of 14 control subjects. In each of 3 protocols, one control failed to develop any evidence for infection. Reasons for these missed infections are unknown. Studies are directed to the identification of either specific or nonspecific inhibitory protein substances in the upper respiratory tract which might be related to humoral defense mechanisms.

ROCKY MOUNTAIN SPOTTED FEVER VACCINE EVALUATION

The study of this disease was initiated in 1967 to evaluate vaccine effectiveness. All of 13 volunteers inoculated intradermally with 10 GPIPID50 doses of the Sheila Smith Strain of Rickettsia rickettsiae developed typical Rocky Mountain spotted fever. Incubation periods averaged 5½ days with a range of 4-9 days. Onset of illness was abrupt with the appearance of fever, headache and myalgia. Rash occurred on the second or third day of fever; its appearance was not inhibited by antibiotics. Chloramphenicol treatment was initiated after 24-36 hr of temperature elevation over 103 F. Therapy with this drug or tetracycline was continued for 5 days. Fever usually abated in 2.5 days after beginning therapy. Five relapses occurred in 3 volunteers treated with chloramphenicol and 2 with tetracycline. The relapse phases were mild and response was prompt on reinstitution of antibiotic therapy.

Studies of rickettsemia are incomplete. Neurologic evaluations have been conducted in the Clinical Study Center of the University of Maryland Hospital. Serial electroencephalograms were normal. One of the 3 patients showed 10 lymphocytes in the spinal fluid at the peak of illness; this cleared promptly.

Two vaccinated volunteers developed illness after the infectious challenge; one had received monovalent Rocky Mountain spotted fever vaccine and the other a composite vaccine including 2 other rickettsial antigens. Studies are in progress and will include various immunizing schedules and a smaller infectious challenge. Complete serologic responses will be determined.

EVALUATION OF ORAL TYPHOID FEVER VACCINES

An oral typhoid vaccine, "Typhoral," which contains 3×10^9 organisms each of typhoid (Ty58), paratyphoid A and paratyphoid B was administered to volunteers in the dosage of 3 tablets/day on 3 successive days. This vaccine has been used by the German Army since 1960. No systemic reactions were noted in 103 volunteers vaccinated in February and March, 1967. One hundred of the volunteers showed the following antibody titers: Somatic (O) 11%, H 3%, and Vi 16%. The titer rises were 4-fold in 60% of the group.

A monovalent Swiss vaccine, "Taboral," containing Salmonella typhi Ty2 (100×10^9 organisms) was given to 88 volunteers in July and December, 1967, in doses of one tablet twice daily for 3 days. No systemic reactions

occurred. Antibody titer responses in 25 subjects were: O antibody 4%, H, 8%, and Vi, 12%. Analysis of the remaining subjects is incomplete.

Eleven volunteers who received "Taboral" vaccine were given 100,000 viable S. typhi (ID₅₀ dose) orally of the Quailes strain in November, 1967. Four of 11, or 36%, developed disease. One of the 4 relapsed and required additional antibiotic therapy; this volunteer had shown Vi antibody following vaccination. The attack rate in volunteers was 38%, which indicates that the killed oral vaccines used are not as effective as the killed vaccines given parenterally.

SIMULTANEOUS INFECTION

The response to simultaneously administered living vaccine strain (LVS) tularemia and Q fever has been studied. The LVS strain of tularemia given by aerosol in large doses, after a 3-day incubation period, produces a mild, self-limiting febrile illness and a prompt serological response. Thirty-five hundred GPIPID₅₀ doses of Q fever rickettsiae is the standardized challenge dose for vaccinated volunteers. Illness in control subjects begins in about 11 days. Several clinical patterns emerged when these organisms were simultaneously aerosolized and inhaled by 17 volunteers. In 7 there was definite synergism: Q fever appeared much earlier than expected. The initial fever caused by LVS did not abate completely. It appeared to blend into a continuous pattern thought due to C. burnetii since there was no response to streptomycin therapy. There was a rapid defervescence following institution of tetracycline. Two separate illnesses were observed in 9 volunteers. One volunteer was given streptomycin with the onset of fever; a second illness did not occur. Serological studies are incomplete. These should clarify the presence of antigenic interference or competition.

STUDIES OF ENDOTOXIN TOLERANCE

Studies of the mechanisms of the acquisition of human endotoxin tolerance were originally designed to evaluate the role of endotoxemia in the pathogenesis of the febrile and toxic course of Gram-negative bacterial infections. (Findings reported previously to the Commission; latest report documented in the Transactions of the Association of American Physicians, 1967; in press.) Focus is now directed to developing methods to combat the effect of overwhelming endotoxemia, i.e., active or passive means of protection. Such studies require further clarification of the mechanisms of endotoxin tolerance.

The importance of antibody in tolerance to endotoxemia is unknown. Quantitative measurements of the febrile and antibody responses of splenectomized rabbits and man to repeated intravenous injections of bacterial endotoxins show that the splenectomized host is no more responsive to the initial injection of endotoxin, yet it develops active and passively transferrable tolerance significantly more slowly than do intact

control subjects. Additional studies were performed in partially hepatectomized rabbits to determine whether such retarded acquisition of tolerance in the splenectomized is based upon decrease in total reticuloendothelial mass or to lack of this major immunologically competent tissue. Despite ablation of a more functional reticuloendothelial system (determined by uptake of Au¹⁹⁸) than in the splenectomized host, no retardation of tolerance was observed. These findings suggest that antibodies do mediate tolerance, and work is currently in progress to characterize these antibodies and quantitate their efficacy during experimental endotoxemia.

TOLERANCE TO STAPHYLOCOCCAL ENTEROTOXIN

Studies initiated at Fort Detrick and continued at the University of Maryland show that SEB is highly pyrogenic for rabbits; fever is probably mediated through the release of endogenous pyrogen. Rabbits vary greatly in their pyrogenic response to an initial intravenous SEB challenge but a dose response relationship can be established. As few as 3 single daily intravenous injections induce a transient pyrogenic refractory state probably mediated by specific sensitization. Repeated intravenous enterotoxin challenge over a period of several months induces a more lasting pyrogenic tolerance probably due to protective serum antibody. Subsequent studies of pathogenesis will attempt to correlate initial pyrogenic sensitivity to enterotoxin and the infectious reaction to the parent staphylococcal strain as well as the effect of enterotoxin desensitization on such infections.

VASCULAR EFFECTS OF CHOLERA TOXIN

A toxic fraction of Vibrio cholera, designated as Craig's permeability factor, has been shown to provoke dilatation of arterioles and sluggish reaction to epinephrine in the rat meso-appendix after oral administration. Further studies of the effect of cholera toxin in the micro-circulation are in progress.

Theodore E. Woodward, M.D.
Director
Commission on Epidemiological Survey

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INTRODUCTION
to the
SYMPOSIUM ON INFECTION AND METABOLISM
Colonel William R. Beisel, MC*

For a period of several years the U. S. Army Medical Unit has looked forward to a meeting that would bring together a key group of investigators for wide-ranging discussions concerning metabolic aspects of infectious illness.

Important facets of the mission of the Medical Unit include: (1) the search for new and improved methods for the rapid diagnosis of infectious illness and (2) the development of methods for the prevention, suppression and/or treatment of infectious illness. Each of these aspects of the mission demands an improved understanding of the mechanisms a normal host employs to resist infection. To achieve these goals a variety of investigative techniques by us, our contractors and others has been used to study metabolic changes within the host. Many of these persons are presenting results of their studies.

It is reasonably sure that information presented during this 2-day session will provide new and exciting concepts concerning the nature and extent of host responses that can be studied with currently available techniques. Many of these studies are quite preliminary in nature at this time, but it is hoped that they may serve as a basis for future advances.

* U. S. Army Medical Unit, Fort Detrick, Maryland.

SECTION I

AMINO ACID AND ENZYME ALTERATIONS IN THE HOST

MODERATOR: Theodore E. Woodward, M.D.

DISCUSSANT: Samuel Bessman, M.D.

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13. ABSTRACT Whole blood amino acids demonstrate a circadian periodicity characterized by values lowest at 0400 hours and highest between 1200 and 2000 hours. They remain relatively stable despite various exogenous and endogenous influences, but are extremely sensitive to infection-induced changes. Studies of carefully controlled infection in human subjects have demonstrated that blood amino acid changes are the earliest and most consistently demonstrable biochemical indication of infection and occur before the onset of clinical illness in the absence of cultural and serological evidence of infectious disease. Changes in periodicity of total blood amino acids, single amino acids, or groups of amino acids have been observed in a variety of infections and may be of value in documenting the presence of infection, in predicting the onset of clinical symptoms, and in studying the pathophysiology of infection-induced metabolic changes in the host.		
14. KEYWORDS: Amino acids Metabolism Infections Circadian periodicity		

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Armed Forces Epidemiological Board
U. S. Army Medical Unit

13. ABSTRACT

The standardization of the systems comprising our avian disease model are discussed. Interactions of diet and disease in the free amino acid pools of liver and muscle are illustrated. Data obtained from continuous sampling at 4-6 hr intervals throughout the incubation stage of a Newcastle disease virus infection in immature cockerels have demonstrated that tissue constituents such as total protein, nucleic and free amino acids may have significant diurnal fluctuations. The patterns, however, are reproducible under controlled environmental and nutritional conditions. Diurnal rhythms observed in infected and control chicks kept under constant lighting may shift completely when the animals are synchronized to a 12-hr light-dark schedule. In the young, rapidly growing chick under the stress of an infection levels of some free amino acids increase while others decrease, suggesting specificity. The relationship between these changes and the phenomenon of periodicity will be discussed.

14. KEYWORDS:

Newcastle disease virus
Amino acids
Diurnal

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11. SUPPLEMENTARY NOTES		12. SPONSORING MILITARY ACTIVITY Commission on Epidemiological Survey Armed Forces Epidemiological Board U. S. Army Medical Unit
13. ABSTRACT Infection of white rats with <u>Pasteurella tularensis</u> and <u>Salmonella typhimurium</u> and exposure to the endotoxin of <u>S. typhimurium</u> stimulated significant changes in various serum enzymes including aldolase, lactate dehydrogenase, phosphohexose isomerase, isocitrate dehydrogenase, glutamate-pyruvate transaminase, glutamate-oxalacetate transaminase, ornithine carbamyl transferase, arginase, acid phosphatase, and alkaline phosphatase. The rates of increase in enzymatic activity were directly related to the size of infecting dose, the type of infective agent employed, and to the severity and focus of infection. Alterations in activity of serum enzymes frequently were demonstrated prior to the appearance of overt clinical symptoms of infection, suggesting the possibility of employing these procedures for early detection of infectious disease.		
14. KEYWORDS: Tularemia Salmonellosis Enzymes		

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4. DESCRIPTIVE NOTES (Type of report and inclusive dates)		
5. AUTHOR(S) (First name, middle initial, last name) MORTON I. RAPOPORT		
6. REPORT DATE September 1967	7a. TOTAL NO. OF PAGES 9 + 8 Figures	7b. NO. OF REFS 7
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11. SUPPLEMENTARY NOTES	12. SPONSORING MILITARY ACTIVITY Commission on Epidemiological Survey Armed Forces Epidemiological Board U. S. Army Medical Unit	
13. ABSTRACT Evidence is presented to indicate that induced pneumococcal infection in mice is capable of producing alterations in liver protein anabolism and a specific model liver enzyme, tryptophan pyrrolase. These changes appear to parallel one another and seem mechanistically related in that intact pituitary-gland function is a requirement for their occurrence. It is shown that the changes in enzyme synthesis and total hepatic protein anabolism occur very early in the course of infection.		
Studies designed to demonstrate the existence or absence of these changes in humans with infectious illness have been performed. It has been shown that the excretion of urinary diazotizable amines is directly related in magnitude to the quantity of tryptophan metabolized through the niacin pathway. Prospective studies of volunteers with sandfly fever indicate that a significant increase in excretion of the amines may occur well in advance of fever and clinical illness.		
14. KEYWORDS:		
<u>Diplococcus pneumoniae</u> Mice Enzymes Sandfly fever		

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10. DISTRIBUTION STATEMENT Each transmittal of this document outside the Department of Defense must have prior approval of Commanding General, U. S. Army Medical Research and Development Command, Washington, D. C. 20315		
11. SUPPLEMENTARY NOTES	12. SPONSORING MILITARY ACTIVITY Commission on Epidemiological Survey Armed Forces Epidemiological Board U. S. Army Medical Unit	
13. ADDITIONAL INFORMATION Evidence is presented to indicate that induced pneumococcal infection in mice is capable of producing alterations in liver protein anabolism and a specific model liver enzyme, tryptophan pyrolase. These changes appear to parallel one another and seem mechanistically related in that intact pituitary-gland function is a requirement for their occurrence. It is shown that the changes in enzyme synthesis and total hepatic protein anabolism occur very early in the course of infection.		
Studies designed to demonstrate the existence or absence of these changes in humans with infectious illness have been performed. It has been shown that the excretion of urinary diazotizable amines is directly related in magnitude to the quantity of tryptophan metabolized through the niacin pathway. Prospective studies of volunteers with sandfly fever indicate that a significant increase in excretion of the amines may occur well in advance of fever and clinical illness.		
14. KEYWORDS:		
<u>Diplococcus pneumoniae</u> Mice Enzymes Sandfly fever		

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SECTION II

CELLULAR NUCLEIC ACID CHANGES DURING INFECTION

MODERATOR: W. Barry Wood, M.D.

DISCUSSANT: Hilton B. Levy, Ph.D.

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3. REPORT TITLE RIBONUCLEIC ACID METABOLISM DURING DISEASE		
4. DESCRIPTIVE NOTES (Type of report and inclusive dates)		
5. AUTHOR(S) (First name, middle initial, last name) J. MICHAEL KEHOE		
6. REPORT DATE September 1967	7a. TOTAL NO. OF PAGES 4 + 6 Figures	7b. NO. OF REFS 1
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11. SUPPLEMENTARY NOTES	12. SPONSORING MILITARY ACTIVITY Commission on Epidemiological Survey Armed Forces Epidemiological Board	
13. ABSTRACT Previous studies from this laboratory have demonstrated time-dependent alterations in protein synthesis in various organs of mice experimentally infected with bacteria or viruses. We have extended these studies, giving particular attention to the effect of the disease state on the utilization by intact mice of a specific RNA precursor. Alterations in the utilization of a specific RNA metabolic precursor have been detected in groups of mice experimentally infected with <u>Diplococcus pneumoniae</u> or Venezuelan equine encephalitis virus.		
14. KEYWORDS: <u>Diplococcus pneumoniae</u> Encephalitis virus (VEG) Mice RNA		

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3. REPORT TITLE NUCLEIC ACID METABOLISM IN THE HUMAN LYMPHOCYTE		
4. DESCRIPTIVE NOTES (Type of report and inclusive dates)		
5. AUTHOR(S) (First name, middle initial, last name) HAMISH N. MUNRO		
6. REPORT DATE September 1967	7a. TOTAL NO. OF PAGES 8	7b. NO. OF REFS 24
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11. DISTRIBUTION STATEMENT Each transmittal of this document outside the Department of Defense must have prior approval of Commanding General, U. S. Army Medical Research and Development Command, Washington, D. C. 20315		
11. SUPPLEMENTARY NOTES		12. SPONSORING MILITARY ACTIVITY Commission on Epidemiological Survey Armed Forces Epidemiological Board U. S. Army Medical Unit
13. ABSTRACT The small lymphocyte is an immunocompetent cell capable <u>in vitro</u> of RNA, protein, and DNA synthesis and of division. When stimulated <u>in vitro</u> with nonspecific "mitogens", e.g., phytohemagglutinin (PHA) the majority of lymphocytes in culture perform all these functions in a greatly accelerated fashion, transforming into enlarged, pyroninophilic (RNA-rich) cells. Through proliferation and differentiation in the body, small lymphocytes probably participate in all aspects of immunity, including protection against infectious disease. Human thoracic duct lymphocytes, uncontaminated with other white cell types, have been used in studies to clarify the biochemical mechanism of transformation, and to link this mechanism with that of immune resistance.		
It has been found that the PHA-stimulated lymphocytes rapidly synthesized new RNA species detectable by labeling the lymphocytes in culture with ^{3}H -uridine. Different species of RNA predominate at different time intervals after exposure to the transforming agent.		
14. KEYWORDS:		
RNA DNA Lymphocytes Tissue culture Protein immunity		

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1. ORIGINATING ACTIVITY (Corporate author) Albert Einstein College of Medicine New York, N. Y. 10461		2a. REPORT SECURITY CLASSIFICATION UNCLASSIFIED
		2b. GROUP N/A
3. REPORT TITLE NUCLEIC ACID SYNTHESIS AND MICROCONTAMINANTS IN TISSUE CULTURE		
4. DESCRIPTIVE NOTES (Type of report and inclusive dates)		
5. AUTHOR(S) (First name, middle initial, last name) ELLIOT M. LEVINE; HARRY EAGLE		
6. REPORT DATE September 1967	7a. TOTAL NO. OF PAGES 4	7b. NO. OF REFS 1
8a. CONTRACT OR GRANT NO.	8a. ORIGINATOR'S REPORT NUMBER(S)	
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11. SUPPLEMENTARY NOTES	12. SPONSORING MILITARY ACTIVITY Commission on Epidemiological Survey Armed Forces Epidemiological Board U. S. Army Medical Unit	
13. ABSTRACT Many cell cultures in laboratory appear to develop profound changes in the pattern of nucleic acid synthesis during their serial propagation. The specific alterations are: Appearance of a new species of RNA; absence of C ¹⁴ -uridine incorporation into ribosomal precursor RNA, and appearance of a new species of DNA. Despite these profound changes in nucleic acid synthesis, the gross appearance, generation time and life expectancy of these altered cultures are not demonstrably affected. Preliminary experiments suggest that inoculation with mycoplasma can produce changes in cell cultures. Studies are continuing as to the nature of mycoplasma-cell interaction in culture with regard to nucleic acid synthesis.		
14. KEYWORDS:		
RNA DNA Nucleic acids Ribosome Protein synthesis Tissue culture		

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1. ORIGINATING ACTIVITY (Corporate author) Collaborative Research, Inc. Waltham, Massachusetts 02154		3a. REPORT SECURITY CLASSIFICATION UNCLASSIFIED
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3. REPORT TITLE THE POSSIBLE USE OF OLIGONUCLEOTIDE ANALOGUES AS VIRAL INHIBITORS		
4. DESCRIPTIVE NOTES (Type of report and inclusive dates)		
5. AUTHOR(S) (First name, middle initial, last name) PAUL C. ZAMECNIK; ORRIE FRIEDMAN		
6. REPORT DATE September 1967	7a. TOTAL NO. OF PAGES 4	7b. NO. OF REFS 1
8a. CONTRACT OR GRANT NO. DA-49-193-MD-2679	9a. ORIGINATOR'S REPORT NUMBER(S)	
8b. PROJECT NO 1B622401A096	9b. OTHER REPORT NO(S) (Any other numbers that may be assigned this report)	
c. Task No. 1B622401A096 02		
d. Work Unit 1B622401A096 02 906		
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11. SUPPLEMENTARY NOTES	12. SPONSORING MILITARY ACTIVITY Commission on Epidemiological Survey Armed Forces Epidemiological Board U. S. Army Medical Unit	
13. ABSTRACT The induction in a host cell of an RNA-dependent RNA polymerase by a virus invader presents a special chemotherapeutic challenge. If an oligonucleotide can be found to inhibit this enzyme while sparing the synthetic action of the normal DNA-RNA polymerase of the cell, the reproduction of the virus may be brought to a halt, while the host is spared. Preliminary experiments toward this goal, employing synthetic oligonucleotides were described.		
14. KEYWORDS:		
RNA DNA Enzymes Nucleotides Leukemia "virus"		

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SECTION III

IMMUNOLOGICAL ASPECTS

MODERATOR: W. Barry Wood, M.D.

DISCUSSANT: James G. Hirsch, M.D.

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3. REPORT TITLE DETECTION OF EARLY ANTIBODY		
4. DESCRIPTIVE NOTES (Type of report and inclusive dates)		
5. AUTHOR(S) (First name, middle initial, last name) ROBERT E. KRISCH		
6. REPORT DATE September 1967	7a. TOTAL NO. OF PAGES 6 + 8 Figures	7b. NO. OF REFS 8
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8e. Task No. 1B622401A096 01		
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11. SUPPLEMENTARY NOTES	12. SPONSORING MILITARY ACTIVITY Commission on Epidemiological Survey Armed Forces Epidemiological Board	
13. ABSTRACT The normal primary immune response has been studied in mice by identifying by the Jerne plaque technique specific antibody-producing cells in spleen (and blood) preparations made at various intervals following antigenic stimulation and by following changes in the numbers of such cells and in the biochemistry of individual cells. Plaque-forming cells have been detected in peripheral blood. There is a definite cellular response in mouse blood to antigenic stimulation. However, the magnitude of the response is much less in the blood than in the spleen. Rate of DNA synthesis of nucleic acids in cell cultures can be studied by autoradiography, using radioactively labeled precursor molecules. Methyl green-pyronin and acridine orange staining have both been used to determine the RNA content of plaque-forming cells. Both of these staining techniques as well as the autoradiographic technique allow comparison of antibody-producing cells with other spleen cells on the same slide.		
14. KEYWORDS: Antibody Immunity Mice Antigens Tissue culture Nucleic acids		

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3. REPORT TITLE EARLY DETECTION OF CIRCULATING ANTIGEN		
4. DESCRIPTIVE NOTES (Type of report and inclusive dates)		
5. AUTHORITY (Print name, middle initial, last name) MARTHA K. WARD		
6. REPORT DATE September 1967	7A. TOTAL NO. OF PAGES 6	7B. NO. OF REPS 5
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11. SUPPLEMENTARY NOTES	12. SPONSORING MILITARY ACTIVITY Commission on Epidemiological Survey Armed Forces Epidemiological Board	
13. AGGREGATE Studies to examine the feasibility of using a rapid agglutination test employing latex particles sensitized with specific antibody to detect circulating antigens early in infection have been recently initiated.		
The preliminary studies reported have been limited largely to work with pneumococcus Type I culture filtrates and infections with this organism in rats. Latex particles treated with antiserum prepared by immunization of rabbits with formalin-killed, capsulated organisms are specifically agglutinated by sterile culture filtrates in relatively high dilutions. A number of factors markedly affect the stability of the sensitized particles and sensitivity of the technique.		
Results of initial experiments with serum specimens collected from infected rats indicate that the use of this technique with clinical specimens shows sufficient promise to warrant further investigation.		
14. KEYWORDS: Agglutination Antibody Detection <u>Diplococcus pneumoniae</u> Rats		

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2. REPORT TITLE		
EARLY CHANGES IN GAMMA GLOBULINS		
3. DESCRIPTIVE NOTES (Type of report and inclusive dates)		
4. AUTHOR(S) (First name, middle initial, last name)		
VIRGINIA G. McGANN		
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7. PROJECT NO. 1B622401A096		8a. ORIGINATOR'S REPORT NUMBER(S)
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10. DISTRIBUTION STATEMENT Each transmittal of this document outside the Department of Defense must have prior approval of Commanding General, U. S. Army Medical Research and Development Command, Washington, D. C. 20315		
11. SUPPLEMENTARY NOTES		12. SPONSORING MILITARY ACTIVITY Commission on Epidemiological Survey Armed Forces Epidemiological Board
13. APPROXIMATELY preliminary investigations in 10 volunteers were initiated to determine whether differential changes in intravascular levels of human IgG, IgM and IgA could be detected shortly after immunization or infection with 17-D strain, yellow fever virus.		
Immunoglobulin changes in 2 control subjects were comparable. Responses of IgG and IgM were cyclic with maximum values at approximately 3-day intervals. IgA decreased after injection to 40-60% below normal. These changes in controls were attributed to blood loss of approximately 760 ml during the study.		
Immunized volunteers showed no characteristic pattern of response: one followed a diurnal rhythm days 1-6, with elevated values thereafter; one with neutralizing antibody but no known prior experience responded like controls. None of the other 6 immunized subjects showed a cyclic response of IgG: 3 had decreases in IgG, and 2 had no change. Markedly elevated levels of IgA were found in plasma from > 50% of immunized men. The IgM response was variable but not significantly different from that of the controls. The effect of blood loss, preinoculation levels of immunoglobulin, liver involvement and antibody development are discussed.		
14. KEYWORDS:		
Immunity Globulin Yellow fever virus Vaccine (17-D)		

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SECTION IV

**INFECTION AND GENERALIZED HOST RESPONSES
HORMONAL RESPONSES**

MODERATOR: Leighton E. Cluff, M.D.

DISCUSSANT: Sidney H. Ingbar, M.D.

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3. REPORT TITLE THYROID HORMONES AND INSULIN		
4. DESCRIPTIVE NOTES (Type of report and inclusive dates)		
5. AUTHOR(S) (First name, middle initial, last name) GEORGE E. SHAMBAUGH, III		
6. REPORT DATE September 1967	7a. TOTAL NO. OF PAGES 8 + 8 Figures	7b. NO. OF REPS 11
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11. SUPPLEMENTARY NOTES	12. SPONSORING MILITARY ACTIVITY Commission on Epidemiological Survey Armed Forces Epidemiological Board	
13. ABSTRACT Studies were undertaken in rats to determine possible alterations in peripheral thyroid hormone physiology during infection with Type I pneumococci. Induced pneumococcal septicemia in the rat resulted in enhancement of hepatic tyrosine transaminase (TT) activity which was dependent upon an intact pituitary adrenal axis. The diminution of hepatic TT response to infection in thyroidectomized rats suggests that thyroxine modulates pituitary adrenal activity and that alterations in thyroid physiology during infection in man may modulate induction of steroid dependent proteins. A peripheral inhibition of insulin action and an alteration in thyroid hormone physiology during acute illness may contribute to the host response to infection.		
14. KEYWORDS: Hormones Insulin Thyroxine <u>Diplococcus pneumoniae</u> Rats Tyrosine transaminase		

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3. REPORT TITLE		
ADRENOCORTICAL RESPONSE AND INFECTIOUS DISEASE		
4. DESCRIPTIVE NOTES (Type of report and inclusive dates)		
5. AUTHOR(S) (First name, middle initial, last name)		
WILLIAM R. BEISEL		
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11. SUPPLEMENTARY NOTES	12. SPONSORING MILITARY ACTIVITY Commission on Epidemiological Survey Armed Forces Epidemiological Board	
13. ABSTRACT As determined in prospective studies involving the exposure of volunteers to several pathogenic microorganisms, the adrenal response to acute infectious illness is rather stereotyped: an increase in glucocorticoid hormone output; plasma 17-OHCS concentrations lose their afternoon diurnal fall; and increases in aldosterone lag behind the glucocorticoid response and coincide in timing with the fall in urinary Na and Cl during infection. Mild infectious illness may fail to produce a detectable adrenal response. Severe or protracted acute infections or chronic infections appear to be associated with a depression of adrenocortical output. While the corticosteroids have been shown to influence in some manner virtually every aspect of the local inflammatory response, phagocytosis, and antibody synthesis, most attempts to ascertain the mechanisms involved have employed high pharmacologic doses. Although it has been assumed that the increased adrenal response during infection contributed importantly to catabolic losses of body protein, an evaluation of current data does not support such a conclusion. Evidence has been obtained in studies of protein synthesis and enzyme induction in experimental animal infections that the endogenous glucocorticoids may be beneficial to the host by stimulating increased protein anabolism, especially within the liver.		
14. KEYWORDS: Adrenal cortex hormones; Adrenal gland; Enzymes; Protein		

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3. REPORT TITLE MUSCLE PROTEIN METABOLISM			
4. DESCRIPTIVE NOTES (Type of report and inclusive dates)			
5. AUTHOR(S) (First name, middle initial, last name) VERNON R. YOUNG			
6. REPORT DATE September 1967	7a. TOTAL NO. OF PAGES 9 + 9 Figures	7b. NO. OF REFS 14	8. ORIGINATOR'S REPORT NUMBER(S)
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12. SPONSORING MILITARY ACTIVITY Commission on Epidemiological Survey Armed Forces Epidemiological Board U. S. Army Medical Unit		13. ABSTRACT The sedimentation of muscle ribosomes in sucrose gradients was studied in intact rats treated with hydrocortisone and insulin and in rats maintained under different dietary conditions. The decrease in polyribosome levels following infection appears to be more marked than that following hydrocortisone administration. Reduced food intake following infection may be an important factor associated with the decreased muscle polyribosomes. No significant difference was observed in turnover of muscle ribosomal RNA measured in rats given adequate or low protein intakes.	
14. KEYWORDS: Ribosomes Muscle protein Nitrogen <u>Salmonella typhimurium</u> Insulin Hydrocortisone			

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SECTION V

INFECTION AND GENERALIZED HOST RESPONSES

WHOLE BODY RESPONSES

MODERATOR: Leighton E. Cluff, M.D.

DISCUSSANT: Charles L. Wisseman, Jr., M.D.

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3. REPORT TITLE THE EFFECT OF HYPERHERMIA ON PROTEIN METABOLISM <u>IN VIVO</u> AND <u>IN VITRO</u> AS OBSERVED IN THE NEW ZEALAND WHITE RABBIT		
4. DESCRIPTIVE NOTES (Type of report and inclusive dates)		
5. AUTHOR(S) (First name, middle initial, last name) IRVING GRAY; SALVATORE LETO		
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11. SUPPLEMENTARY NOTES	12. SPONSORING MILITARY ACTIVITY Commission on Epidemiological Survey Armed Forces Epidemiological Board U. S. Army Medical Unit	
13. ABSTRACT The effect of fever on protein metabolism has not been closely examined previously. We have studied the effect of hyperthermia on protein metabolism in rabbits by both <u>in vivo</u> and <u>in vitro</u> techniques using L-methionine-S ³⁵ and S ³⁵ -labeled serum protein.		
A subcellular explanation for this increased catabolic activity directed attention to cathepsins. Lysosomes were isolated from livers of control and hyperthermic rabbits. Both control and experimental lysosomal cathepsins were found to have an optimum pH of 5, and showed a 4-fold increase in activity with the addition of -SH groups (cysteine). The activity of both groups was seen to follow expected temperature kinetics, higher at 41 C than at 37 C. The proteolytic activity of the experimental group was markedly increased in the breakdown rate.		
Apparently, a major effect of fever is to depress protein synthesis, and at the same time, increase the rate of breakdown of host protein by temperature and feedback stimulation of catabolic activity. The increase in proteolytic activity may be a result of temperature activation of inactive enzymes and an increase in turnover number at the higher temperature.		
14. KEYWORDS: Cathepsins Hyperthermia Proteins Rabbits Radioisotopes		

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5. AUTHOR(S) (First name, middle initial, last name) DAVID G. Van ORMER		
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11. SUPPLEMENTARY NOTES	12. SPONSORING MILITARY ACTIVITY Commission on Epidemiological Survey Armed Forces Epidemiological Board	
13. ABSTRACT Recent improvements in methodology make it possible to detect and quantitate many of the trace elements in biological fluids despite their low concentrations. Urinary Zn was selected for initial study because it could be detected by atomic absorption spectroscopy without the need for prior concentration or extraction. Following challenge of normal volunteers with <u>Pasteurella tularensis</u> , an early fall in urinary Zn excretion accompanied the onset of symptoms and fever; this early drop was followed by a marked and prolonged increase. Similarly in subjects exposed to <u>Coxiella burnetii</u> , little change in urinary Zn occurred in the early portions of the long incubation period; then it showed a presymptomatic fall followed by a postfebrile rise.		
Preconcentration, digestion procedures, chelation, and solvent extraction are currently under investigation to provide for a future method that will be precise, rapid, consistent and relatively simple for other trace elements.		
14. KEYWORDS: Trace elements Zinc Tularemia Q Fever		

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5. AUTHOR(S) (First name, middle initial, last name) ALBERT S. KLAINER		
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11. SUPPLEMENTARY NOTES	12. SPONSORING MILITARY ACTIVITY Commission on Epidemiological Survey Armed Forces Epidemiological Board	
13. ABSTRACT Serum glycoglobulin changes in infection appear to occur earlier and may be more specific than changes in routine serum proteins. Experimentally induced pneumococcal infection in mice and rats resulted in a significant decrease in α_1 -glycogobulin within 12-16 hr postinfection. Respiratory-acquired tularemia in humans, on the other hand, resulted in significant increases in α_1 -glycoglobulin just prior to, or simultaneous with, the appearance of clinical illness. Further studies are in progress to elucidate further the role of these serum proteins in the metabolic response of the host to infection. In addition there is some evidence that characteristic patterns may evolve for specific infections.		
14. KEYWORDS: Serum globulins Glycoproteins Tularemia <u>Diplococcus pneumoniae</u>		

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5. AUTHOR(S) (First name, middle initial, last name) PAUL M. NEWBERNE		
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11. SUPPLEMENTARY NOTES		12. SPONSORING MILITARY ACTIVITY Commission on Epidemiological Survey Armed Forces Epidemiological Board U. S. Army Medical Unit
13. ABSTRACT In order to test the influence of caloric intake on resistance to infection beagles were divided into groups and fed balanced diets supplying varying numbers of calories. Commensurate weight changes resulted in 5 or 6 weeks. Dogs were exposed to distemper virus by intracerebral inoculation. Determinations for N and blood chemistry were made pre- and postexposure. High-fed animals had the highest mortality. Accumulative N loss was greater and occurred sooner in the high-fed group; clinical responses were severe and in most paralytic encephalitis appeared in 8-10 days. Serum antibody titers did not correlate with resistance to the virus or with survival.		
Preliminary results indicate that obesity has a profound effect on the response of the endocrine system of the dog infected with distemper virus. It is concluded that obese dogs have less resistance to distemper infection and that this decreased resistance is related in some obscure way to protein metabolism and hormone balance.		
14. KEYWORDS: Distemper virus Diet Dogs Nitrogen balance Serum cortisol Protein-bound iodine Lipids Obesity		

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SECTION VI

BACTERIAL TOXINS

MODERATOR: J. Vernon Knight, M.D.

DISCUSSANT: Elisha Atkins, M.D.

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4. DESCRIPTIVE NOTES (Type of report and inclusive dates)		
5. AUTHOR(S) (First name, middle initial, last name) SHELDON E. GREISMAN; EDWARD J. YOUNG; FRANK A. CAROZZA, JR.; JOSEPH B. WORKMAN		
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11. SUPPLEMENTARY NOTES	12. SPONSORING MILITARY ACTIVITY Commission on Epidemiological Survey Armed Forces Epidemiological Board U. S. Army Medical Unit	
13. ABSTRACT Rabbits were splenectomized and later challenged with <u>Escherichia coli</u> endotoxin. Marked effects were noted in acquisition of pyrogenic tolerance as compared to sham-operated animals. In the same animals O antibody was not produced, although controls developed increasing titers. Development of pyrogenic tolerance and O antibodies were observed in men with and without spleens. Only the late phase of tolerance was tested because of early toxicity. Men with no spleens were unable to elaborate O antibodies; there was concomitant retardation of pyrogenic tolerance development.		
14. KEYWORDS: <u>Escherichia coli</u> Endotoxin Rabbits Man Pyrogens		

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4. DESCRIPTIVE NOTES (Type of report and inclusive dates)		
5. AUTHOR(S) (First name, middle initial, last name) PETER F. BONVENTRE; J. C. IMHOFF		
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13. ABSTRACT By two independent methods of analysis (microdensitometry of tissue autoradiograms and radioactivity of tissue proteins), the effect of the diphtheria toxin on incorporation of H-leucine into protein <i>in vivo</i> was evaluated in guinea pigs and mice. In guinea pigs it was found that inhibition of protein synthesis was not a generalized metabolic effect of the toxin but rather seemed to be restricted primarily to cardiac tissues, (75% near normal elsewhere). No inhibition of protein synthesis was seen in any tissues of the resistant mouse.		
In order to determine if species sensitivity or resistance was reflected under conditions where the cardiac tissues were removed from neural and endocrine influences primary heart cell cultures derived from embryonic guinea pigs and neonatal rats were exposed to diphtheria toxin and examined with respect to protein synthesis and morphological changes.		
Guinea pig heart cell cultures were found to be extremely sensitive to the toxin: 50% inhibition even with small quantities of toxin; and a cytopathic effect. Rat heart cells were unaffected. The results show that the heart cells reflect species resistance or sensitivity in the absence of neural or endocrine influences and suggest further that the toxin exerts a direct toxicity to muscle cells of the heart.		
14. KEYWORDS: Diphtheria toxin Tissue culture Protein synthesis		

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4. DESCRIPTIVE NOTES (Type of report and inclusive dates)		
5. AUTHOR(S) (First name, middle initial, last name) SIGURD J. NORMANN		
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11. SUPPLEMENTARY NOTES		12. SPONSORING MILITARY ACTIVITY Commission on Epidemiological Survey Armed Forces Epidemiological Board
13. ABSTRACT Experimental enterotoxemia was induced in rats and monkeys by intravenous injection of purified staphylococcal enterotoxin B. The clearance of the toxin from the blood and its biologic distribution were examined. Differences in clearance rate were found depending on the means by which the toxin was identified since I^{125} -labeled toxin was cleared at a faster rate than toxin labeled with fluorescein isothiocyanate. In both instances the toxin was rapidly removed from circulation principally by means of renal clearance. This conclusion was supported by distribution studies and by the dramatic drop in clearance rate as a result of nephrectomy. Distribution of the toxin was studied in relation to its concentration in whole organs by means of radioactivity and to its cellular localization by means of fluorescence microscopy. Fluorescent labeled and unlabeled toxin identified by fluorescent antibody methods was consistently seen only in proximal convoluted tubules, although low amounts of radioactivity were detected in liver and gastrointestinal tract. It was proposed that toxin gained access to these tubules by a process of glomerular filtration and tubular reabsorption.		
14. KEYWORDS: Enterotoxin B, staphylococcal Toxemia Kidney Rats Monkeys Fluorescence Radioisotopes		